OXYGEN SUBSTITUTED DERIVATIVES OF NUCLEOPHILE-NITRIC OXIDE ADDUCTS AS NITRIC OXIDE DONOR PRODRUGS

This application is a continuation-in-part of copending patent application Ser. No. 07/764,908 filed Sep. 24, 1991 now abandoned.

FIELD OF THE INVENTION

The present invention generally relates to the treatment of patients suffering from cardiovascular disorders requiring a lowering of the blood pressure. Certain novel compounds and pharmaceutical compositions which release nitric oxide on in vivo activation are utilized in the method.

BACKGROUND OF THE INVENTION

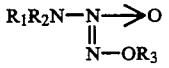
Endothelium-derived relaxing factor (EDRF) is a labile humoral agent which is part of a cascade of interacting agents involved in the relaxation of vascular smooth muscle. EDRF is thus important in the control of vascular resistance to blood flow and in the control of blood pressure. Some vasodilators act by causing EDRF to be released from endothelial cells. (See Furchgott, Ann. Rev. Pharmacol. Toxicol. 24, 175–197, 1984.) Recently, Palmer et al. have presented evidence suggesting that EDRF is identical to the simple molecule, nitric oxide, NO (Nature 317, 524–526, 1987), though there remains controversy on this point. It has been hypothesized for years that many nitrovasodilators that mimic the effect of EDRF, like glyceryl trinitrate, amyl nitrite, $NaNO_2$, and sodium nitroprusside (SNP), do so by virtue of their conversion to a common moiety, namely NO, which is also a vasodilator. (See Kruszyna et al., Tox. & Appl. Pharmacol. 91, 429–438, 1987; Ignarro, FASEB J. 3, 31–36, 1989; Ignarro et al., J. Pharmacol. Exper. Therapeutics 218 (3), 739–749, 1981.)

Some of the compounds suitable for use in the method of the present invention are previously described in scientific literature. However, there is no suggestion in the prior art that any of the disclosed compounds are antihypertensive; indeed there is no suggestion in the prior art that they have any pharmaceutical use. Four compounds are described in Reilly, U.S. Pat. No. 3,153,094, and in Longhi and Drago, Inorg. Chem. 2, 85–88, 1963, and four compounds are disclosed in Artsybasheva and Ioffe, J. Org. Chem. U.S.S.R. (Engl. transl., 23, 1056–1060, 1987). Each of these references is incorporated by reference herein in its entirety. The references teach no biological activity for the compounds disclosed.

Related inventions (to the present invention) are described in U.S. patent application Ser. Nos. 07/316,958, filed Feb. 28, 1989 (now U.S. Pat. No. 4,954,526), 07/409,552, filed Sep. 15, 1989 (now U.S. Pat. No. 5,039,705), 07/423,279, filed Oct. 18, 1989, 07/585,793, filed Sep. 20, 1990, 07/743,892, filed Aug. 12, 1991, 07/764,906, filed Sep. 24, 1991, 07/764,908, filed Sep. 24, 1992, 07/858,885, filed Mar. 27, 1992, 07/867,759, filed Apr. 18, 1992, and 07/935,565, filed Aug. 24, 1992, each of which is incorporated herein by reference.

SUMMARY OF THE INVENTION

It has now been discovered that a class of compounds of the structure:



wherein R_1–R_3 are organic moieties defined below, are long-acting cardiovascular agents and thus are useful for treating cardiovascular disorders in which lowering the blood pressure has a beneficial result. It is believed that these compounds function by metabolic cleavage of the R_3 group to produce an anion that releases NO in the blood after administration to a mammal; however, the invention should not be limited by this hypothesis.

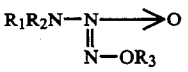
The present invention will become more fully understood from the detailed description given here and below and the accompanying drawing which is given by way of illustration only, and thus is not limitative of the present invention.

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1—shows the dose response curve for Et_2-N—N(O)NOEt, which was obtained by testing the compound via a standard isolated vascular ring preparation.

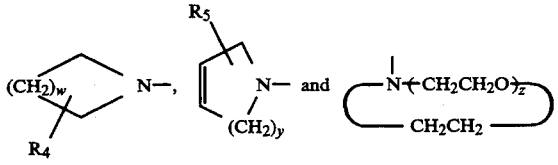
DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for pharmaceutical compositions comprising a compound of formula I,



(I)

wherein R_1 and R_2 are independently chosen from C_{1-12} straight chain alkyl, C_{1-12} alkoxy or acyloxy substituted straight chain alkyl, C_{2-12} hydroxy or halo substituted straight chain alkyl, C_{3-12} branched chain alkyl, C_{3-12} hydroxy, halo, alkoxy, or acyloxy substituted branched chain alkyl, C_{3-12} straight chain olefinic and C_{3-12} branched chain olefinic which are unsubstituted or substituted with hydroxy, alkoxy, acyloxy, halo or benzyl, or R_1 and R_2 together with the nitrogen atom to which they are bonded form a heterocyclic ring selected from the group consisting of:



wherein w is 1 to 12, y is 1 or 2, z is 1 to 5, R_4 is hydrogen, C_{1-8} straight chain alkyl, C_{3-8} branched chain alkyl, C_{3-8} cycloalkyl, unsubstituted or substituted aryl, such as phenyl, tolyl or the like, and R_5 is hydrogen, C_{1-6} straight chain alkyl or C_{3-6} branched chain alkyl; and R_3 is a group selected from C_{1-12} straight chain and C_{3-12} branched chain alkyls which are unsubstituted or substituted by hydroxy, halo, acyloxy or alkoxy, C_{2-12} straight chain or C_{3-12} branched chain olefinic which are unsubstituted or substituted by halo, alkoxy, acyloxy or hydroxy, C_{1-12} unsubstituted or substituted acyl, a sulfonyl, sulfinyl, sulfenyl, or carbonate derivative, and a carbamate derivative, as for example, car-